Medical Staff Conference

Osteoporosis

Part II. Prevention of Bone Loss and Fractures in Women and Risks of Menopausal Estrogen Therapy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *In the first part of this symposium on postmenopausal osteoporosis, Dr Henry Genant described the important advances made in quantifying bone density in vivo. Now Dr Gilbert Gordan will discuss the treatment—or, more accurately, the prevention—of this serious form of osteopenia. This is a topic to which Dr Gordan has devoted many years of clinical research and an area in which he has been a major contributor.*

DR GORDAN:† Osteoporotic fractures, occurring with little or no trauma, become extremely frequent in women after menopause or oophorectomy. It is now established from direct measurements of bone mass and from epidemiologic studies that the cause of this serious public health and human problem is estrogen deficiency. Formerly little attention was paid to osteoporosis, but now, with increasing longevity, especially in women, the magnitude, expense and—most important—the preventability of this disease are becoming evident. A prophylactic program is feasible to prevent this hazard to the largest growing segment of our population, elderly women.

Early Observations of Osteoporosis

Osteoporosis is an ancient disease that has only recently become a prominent public health problem, largely because of demographic changes in our population coupled with improved diagnostic methods and better health care in the population as a whole. There are many historical references to osteoporosis. In 1824, for example, Sir Astley Cooper noted from observations at autopsy that in old age "the bones become thin in their shell and spongy in their texture." In 1881 Bruns noted that after age 50, fractures of the wrist and hip occur much more frequently in women than in men. This observation perplexed him because fracture was equated with trauma, and in those days men certainly had more occupational exposure to trauma than did women. But in the 19th century this condition of frequent fractures and loss of height was merely a puzzling curiosity. Not very many women lived long past the menopause (the average age of natural menopause at 50 has remained almost constant in northern and western Europe and the United States for centuries). The major health hazards for women even as recently as 50 years ago were, of course, infectious diseases and the dangers of childbearing; maternal and infant mortality was high. Relatively few lived long enough to be afflicted with the degenerative diseases of the aged that now demand most of our care and attention. The phenomenal advances of modern medical research and health care, which many of us experienced firsthand, have produced dramatic shifts in our population. Americans today are living longer and are, on the average, healthier than ever before, but we are no longer a young nation. The consequence is an ever greater demand on our diminishing pool of health care resources. We are already faced with the difficult ethical dilemma of deciding which patients are to receive the very expensive new therapies made possible by our remarkably sophisticated medical research. Our emphasis now, more than ever before, must be to pay more than lip service to *preven-*

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†Gilbert S. Gordan, MD, PhD, Professor of Medicine, University of California, San Francisco.

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tion of disease, whenever this is possible, rather than focusing almost all of our attention on treatment.

Elderly women comprise the fastest growing group in our population. American women today outlive men by about ten years and can expect to live 40% of their lives after menopause. The human female is the only mammal that outlives reproductive capability. Socially, elderly women are an important and valuable resource with the potential for high productivity to the community as long as they are not impaired by degenerative disease. Few of the degenerative diseases of aging are preventable, but an important one, postmenopausal osteoporosis, is potentially so.

Racial and Sexual Characteristics

It is now established that white-, yellow- and brown-skinned women lose bone rapidly after menopause, so that by age 70, these women have on the average lost 50% of their peripheral cortical bone mass. While black women do lose some bone with aging, this loss is small compared with other ethnic groups and when imposed on a denser skeleton rarely produces pathologic osteoporosis. The mechanism of this genetic protection enjoyed by black women is not yet known; we do know, however, that black women have a much lower incidence of fracture and when fractures occur they are almost exclusively associated with significant trauma.

The sexual dimorphism of bone loss is pronounced. Men of all races at all ages have denser skeletons than women and bone density parallels skin color: black men having the most dense bones and white women the least. Drs Silvia and Eric Meema, in a study of white men in Toronto, Canada, showed that men do not have significant age-related bone loss until around age 70 and the relatively few men in their study who survived to age 95 lost only about 25% of the normal adult male bone mass.[1] In contrast, these authors and others have shown that bone loss in women starts much earlier in life and is biphasic. There is a rapid loss in the first six to ten years after natural menopause—earlier in the case of women who have had oophorectomies—and then a slower, progressive rate of bone loss thereafter. Thus, women who start out with less dense skeletons begin losing bone quite early in life, have a rapid acute phase of bone loss following loss of gonadal function and then continue to lose bone slowly for the rest of their life. Women with a natural menopause at around age 50 can now expect to live another 32 years. It follows, therefore, that unless prophylactic measures are taken to prevent or arrest this inexorable wasting of the skeleton, most women can also expect during the postmenopausal period to lose, overall, 1% to 2% of their peripheral cortical bone each year and much greater amounts of axial bone mass. By age 80, a third to two thirds of the entire skeleton has irretrievably disappeared.

The clinical importance of bone loss of this magnitude is that with enough time (more critical for younger women undergoing bilateral oophorectomy) the skeleton becomes so rarefied and fragile that it is not capable of withstanding normal, or slightly increased, biomechanical stress. In these women vertebral compression fractures are common following a bumpy automobile trip or bending over to pick up a grandchild or even a sudden sneeze. The relationship between pathologic osteoporosis and hip fractures in elderly women is well documented. As shown in Figure 1, elderly women with hip fracture have all lost a significant amount of cortical thickness compared with average postmenopausal values. Some of these women have only 200 mg of hydroxyapatite per sq cm of bone remaining; this is contrasted with a normal value of 700 mg per sq cm found in younger women, which means a loss of more than two thirds of their total skeletal mass. We now see a continuity between what has been called "physiologic" bone loss, meaning that we all lose some bone with aging, and "pathologic" bone loss, because fracture is obviously pathologic. Or, as our patients have been telling us for years, "No, doctor, I did *not* fall down and break my hip; my hip gave way and I fell down."

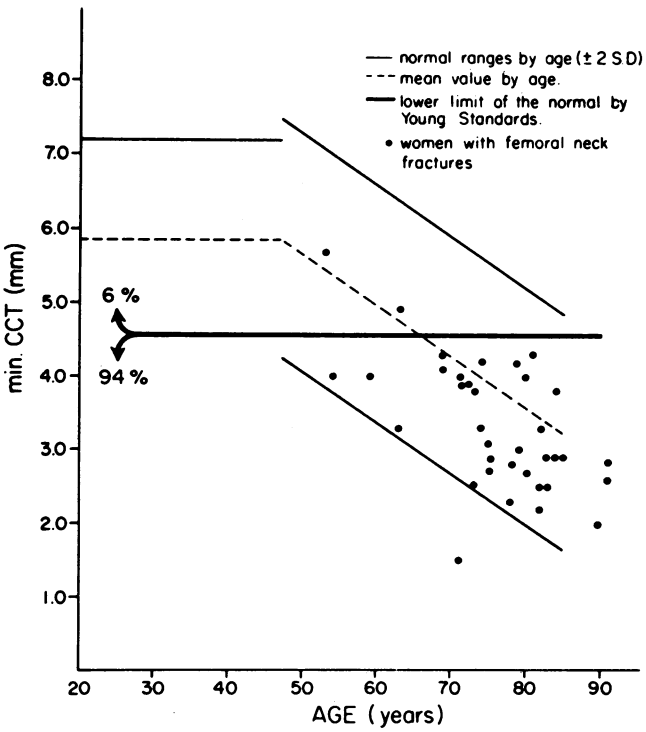

Figure 1.—Minimal combined cortical thickness (CCT) of radius in 36 women who had femoral neck fractures in relation to normal range (from Meema and Meema[1]).

Hip fracture is the ultimate insult to postmenopausal women, occurring usually after 20 or more years of insidious bone loss and vertebral deformity. In all but black women, the incidence doubles every five years after age 50, so that women in their 80s have a 40% chance of having sustained one or more hip fractures. Hip fractures are associated with a high incidence of morbidity and mortality. They do not heal spontaneously, require anesthesia and surgical repair and may result in complications of thromboembolism, pneumonia or congestive heart failure. Many of the patients,

though active before their fracture, never walk again. As the population of elderly women increases, patients who have hip fracture will continue to require ever greater amounts of health care resources for their medical and nursing care. The dollar cost of treating patients with hip fracture is now more than $1.4 billion a year, most of it paid by Medicare funds. The US Vital Statistics on hip fracture have been available only in the past three years; they show that two thirds of the deaths resulting from hip fracture occur in white women over the age of 65. In short, hip fractures cause more deaths than handguns. The good news is that the bone loss that causes most hip fractures is preventable; deaths from handguns are a much more difficult problem to solve. Three case-control studies show that estrogens protect against hip and wrist fractures in elderly women.[2-4] Protecting these women against skeletal fragility not only prevents a painful, disabling disease but saves society billions of dollars in health care and rehabilitation costs. I often think when I listen to politicians talk about our country's need to cut costs in medical care that this would be an excellent place to start. Of course, a billion dollars may not seem like very much compared with a defense budget of $239 billion but, as the late Senator Dirksen pointed out, "a billion here, a billion there, and the first thing you know, you're talking about real money."

Dr Genant noted that the important underlying cause of fractures—bone loss—is now readily and accurately measurable by noninvasive techniques. The precision of the computed tomographic scanning technique is a distinguished contribution to the early detection of postmenopausal bone loss. In a study from Copenhagen, derived from 315 healthy women in early menopause, Christiansen and co-workers have shown that peripheral bone loss precedes fracture by nine or ten years.[5] Dr Genant's measure of vertebral spongiosa steepens the slope of bone loss by a factor of 7 so that it is now feasible, for the first time, to detect insidious, painless bone loss in persons years before fractures occur, just as we recognize and treat glaucoma before optic atrophy and blindness, or diagnose and treat hypertension to prevent myocardial infarction or stroke.[6]

The earliest complication of postmenopausal bone loss is crush fractures of weight-bearing vertebrae. These fractures cluster after age 50 and are associated with statistically significant loss of peripheral bone measured in the radius, while the vertebral spongiosa is visibly depleted. You see women with vertebral crush fractures everywhere. They are bent over with kyphosis, walking painfully with a wide base, desperately edging their way through the traffic of San Francisco, Honolulu, London or Tokyo. In fact, all ethnic groups are represented except blacks. I would like to emphasize the importance of loss of height as a diagnostic factor. Accurate height measurement is best obtained with the simplest equipment—a tape measure tacked to the wall and any rigid object such as a chart, book or ruler used as a right angle. The important thing is to have the patient, without shoes, stand as straight as she can, heels together and her head level. Women who have had vertebral compressions may have twinges of back pain that are worrisome to them and to their doctors because this may indicate another fracture. Each vertebral crush fracture is usually associated with a loss of 1 cm or more of height. Therefore, if there is an accurate baseline height, an additional fracture is easily excluded without the expense of x-ray films or unnecessary exposure to radiation. It is useful, therefore, when one first sees a woman with osteoporosis to estimate her previous height, both from her memory and from comparison of her height with measurement of her arm span. The famous drawing by Leonardo da Vinci, known as the Canon of Proportions, shows his fascination with the following statement of Vitruvius Pollio in *De Architectura,* written about 26 BC: "If we measure from the sole of the foot to the top of the head, and apply the measure to the outstretched hands, the breadth will be found equal to the height." Except in healthy black persons (who have long arms and legs) or in patients with hypogonadism or arachnodactyly, this relation is usually valid within half an inch. A word of warning, do not rely on stadiometers attached to weight scales; these are often quite inaccurate. In patients with vertebral crush fractures, precision of measurement is essential both to estimate previous height loss and to evaluate therapy. Effective treatment prevents further loss of height.

The Importance of Estrogen in Bone Loss

The most important study showing the importance of estrogen in preventing bone loss after oophorectomy in younger women was reported by Lindsay and associates in 1976.[7] In this study the bone mass of 120 women was measured by photon absorptiometry in the metacarpal bones at two sites. Using a double-blind technique, 63 of the women were given mestranol, 20 μg daily (the amount found in the lowest dose oral contraceptives in this country), and 57 were given a placebo. The women taking the placebo lost bone steadily throughout the first five years of the study, whereas the women taking mestranol were protected. This study is being continued. At the end of ten years it was found that the placebo-treated women continued to lose bone mass, had an average height loss of 1.5 cm and showed evidence of vertebral wedging. In contrast, the estrogen-treated women at ten years had the same bone mass as at the beginning of the study, had not lost height and showed no evidence of vertebral wedging. This is a nonintervention study. In contrast, in our studies we do not merely observe bone loss; we use a crossover design so that when a woman has lost a significant amount of bone, she is advised to cross over to an effective dose of estrogen.

Bones do not contain estrogen receptors, therefore, it is a point of considerable theoretical interest how estrogens affect bones. Klotz at l'Hôpital Beaujon-Clichy in Paris was the first to point out in 1975[8] that calcitonin levels in postmenopausal women and in

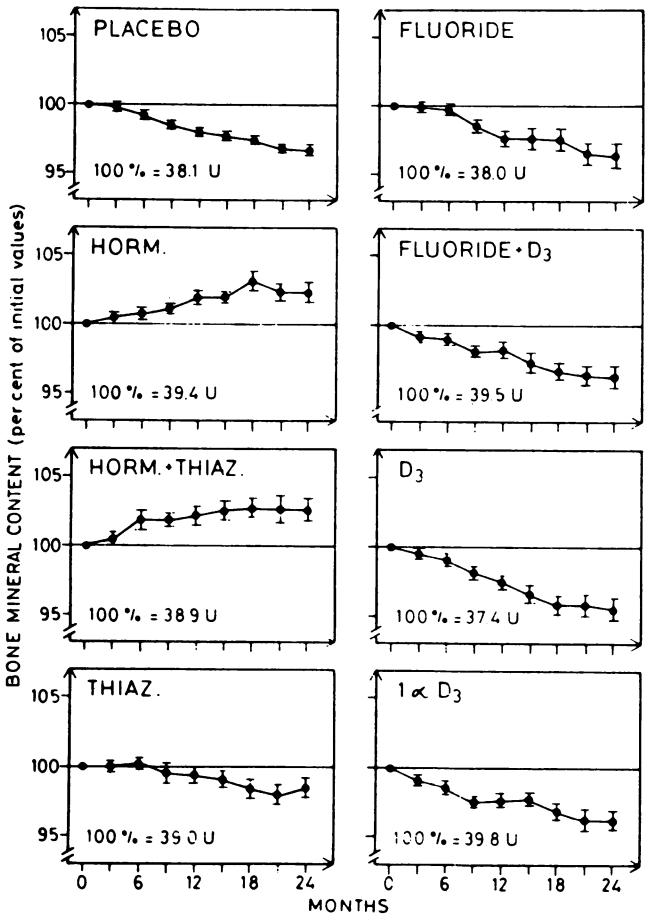

Figure 2.—Bone mineral content measured by photon absorptiometry of distal forearm in 315 healthy women 0.5 to 3 years after last menstrual period (from Christiansen et al[5]). Horm = hormones (estradiol, 4 mg, plus estriol, 2 mg, plus norethisterone acetate, 1 mg, in 28-day cycles); fluoride = sodium fluoride, 20 mg daily; D_3 = vitamin D_3, 2,000 IU a day; $1\alpha D_3$ = 1 α-hydroxyvitamin D_3, 0.25 μg daily; all subjects also received calcium gluconate to provide 1 gram of calcium a day.

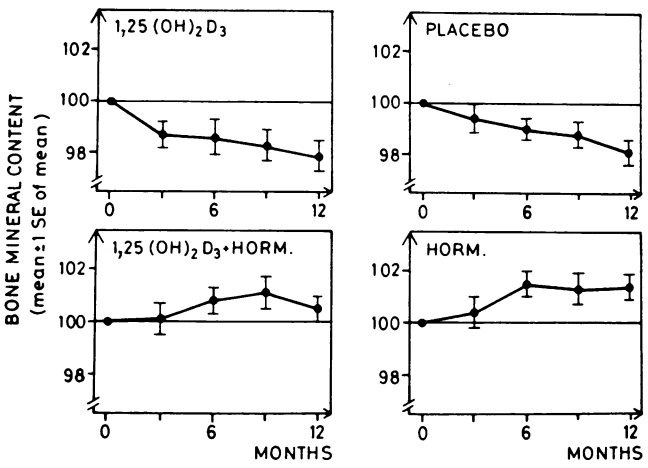

Figure 3.—Changes in bone mineral content (photon absorptiometry of distal forearm) during one year of therapy in 92 normal women 2.5 to 5 years after last menstrual period (from Christiansen et al[14]). Horm = hormones (estradiol, 4 mg, plus estriol, 2 mg, plus norethisterone, 1 mg, in 28-day cycles); 1,25 $(OH)_2D_3$ = 1,25-dihydroxyvitamin D_3, 0.25 μg daily; all participants also received 500 mg of calcium a day.

castrated rats are very low, and they can be raised by administering estrogen. This work has now been confirmed by Milhaud in Paris[9] and by Hillyard[10] and Stevenson[11] and associates in MacIntyre's laboratory in London. Another important mechanism is more controversial—activation of renal 1α-hydroxylase by estrogen. It has long been known that calcium absorption is poor in elderly women. The elegant studies of Heaney and associates[12] in Omaha show that calcium balance after the menopause can only be maintained by very large doses of calcium given orally, whereas estrogen-treated women remain in balance on much smaller dose regimens. Gallagher and co-workers have reported that serum 1,25-dihydroxyvitamin D_3 levels in postmenopausal women are low and that they rise to normal during estrogen treatment.[13] Stevenson and Christiansen have not been able to confirm these findings[5,11] but considering the difficulties with present measurements of 1,25-dihydroxyvitamin D_3, the matter is not closed. In any event, it is clear that estrogen-treated postmenopausal women maintain calcium balance at lower levels of calcium intake than untreated women.

A large number of studies have been carried out to see whether vitamin D, its metabolites and various other agents would prevent or reverse bone loss in postmenopausal women. Christiansen's extensive and careful studies have shown (Figures 2 and 3) that whereas the hormones estradiol and norethisterone acetate prevented bone loss equally well, vitamin D or 1α-vitamin D were not any better than a placebo, and neither 1,25-dihydroxyvitamin D_3 nor fluoride was of any value. I would also emphasize that the latter two are toxic. Adding 1,25-dihydroxyvitamin D_3 to either of the hormone therapies produced results not quite as good as either hormone alone while, of course, adding considerably to the cost of treatment and increasing the risk of hypercalciuria and hypercalcemia.[14]

Despite the volume of data now accumulated from various sources showing the efficacy of estrogen replacement therapy in maintaining skeletal integrity in the postmenopausal woman, a recent survey in the United Kingdom showed that whereas gynecologists consistently treat postmenopausal osteoporosis with hormones, only half the internists do.[15] In this country, gynecologists and family practitioners are receptive to the evidence that postmenopausal osteoporosis is the consequence of estrogen deficiency, whereas the internists are somehow more susceptible to the blandishments of vitamin D and fluoride. Frankly, I do not understand this.

Other Ways of Preventing Osteoporosis

I am often asked if exercise will prevent postmenopausal osteoporosis. While immobilization is obviously bad for bones and all other systems, there is no present evidence to show that exercise alone can replace estrogen for postmenopausal women. The recent findings

that some young women health enthusiasts become amenorrheic, lose bone and sustain fractures strongly suggest that exercise alone is not enough.

In preventing bone loss and fractures we should not overlook the importance of such safety measures as removing the well-named "throw" rugs, obstacle courses of electric wires or long telephone cords and similar hazards. In addition, installing grab bars in bathtubs and showers, sturdy handrails on stairways and good lighting helps prevent falls and minimize trauma. We also tell elderly osteoporotic patients not to pick up heavy objects such as shopping bags or suitcases, to limit themselves to lifting items weighing less than 4.5 kg (10 lb) and to get accustomed to using a shopping cart or similar device not only for shopping but also around the house and garden. Rearranging kitchens and work patterns can also do much to minimize bending and can reduce backaches.

There are four salient, independent risk factors for osteoporotic fractures: being female, lacking gonadal function, not being black and not taking antiosteolytic agents which include estrogens, gestogens, calcium, anabolics or calcitonin. Smoking cigarettes contributes indirectly to osteoporosis by causing an earlier menopause and decreased body fat. Leanness is a contributing factor because adipose tissue contains aromatase that converts the adrenal androgen, androstenedione, to estrone. No one is advocating obesity, however; fat may be good for bones but it is bad for longevity. Our image of the typical osteoporotic patient is a lean, small-boned woman. This is partly because thin women have low blood estrone levels and because there just are not many old fat women.

The prevalence of bone loss in postmenopausal women and women who have had oophorectomies is clearly shown in our study in which 30 of 31 women who received less than 0.6 mg of conjugated estrogens daily lost a significant amount of vertebral spongiosa.[6] Clearly, in these younger women (less than 50 years of age) the risk factor was loss of gonadal function. In this study we found that the minimal effective dose of conjugated estrogens, 0.6 mg, protected five of six women. Christiansen in his study of women who had a natural menopause has also obtained a dose response to estradiol cycled with norethisterone acetate.[4] Those taking the placebo lost bone, 1 mg of estradiol a day reduced the rate of bone loss, 2 mg daily produced a slight gain in bone mass and 4 mg daily produced a greater gain. The optimal protective dose in this study, therefore, was 2 mg daily of estradiol. The Scottish women in Lindsay's study who gained a very small amount of bone mass in their first five years of estrogen replacement therapy did not maintain that gain in the next five years. They did, however, maintain their premenopausal, pretreatment values.[7] You cannot replace much bone tissue after it is lost, hence the importance of *prevention* in postmenopausal osteoporosis.

We have shown in a long-term study, with follow-up for more than 30 years, that pathologic osteoporosis can be arrested and further fractures prevented, even when the disease is far advanced. This has only been shown with full replacement doses of estrogen—that is, 1.25 mg of conjugated estrogens, or 50 μg of ethinyl estradiol, or 1 mg of stilbestrol or 6 mg of methallenestril for 21 to 25 consecutive days each month. We also recommend adding a progestin for the last ten days of the estrogen cycle, with a hiatus of five to seven days each month without hormones. On this regimen we prepare our patients to expect a period of withdrawal bleeding for three to five days during the time they are not taking the hormones. Our experience with compliance has been excellent, largely because from the start we take the time with each of our patients to explain the rationale of treatment and what they can expect and we encourage them to ask questions. Patient education is an essential part of the treatment.

Although the ideal treatment of estrogen deficiency is replacement with oral estrogens in the lowest effective dose, it is clear that not all women can or should receive estrogen therapy. Clear contraindications are, of course, a history of breast cancer or invasive endometrial cancer, bleeding uterine fibroids, migraine or congestive heart failure. The most common reason for women refusing estrogen replacement therapy is cancerphobia, which is primarily caused by sensational and often inaccurate or incomplete reports in the mass media. Fortunately for our patients, we now have good data to show that bone loss can be prevented by several other methods: progestational agents; large doses of calcium taken orally, anabolics or frequent injections of calcitonin. With this information, we now have ample ways to prevent postmenopausal bone loss and women need no longer be condemned to osteoporotic fractures of the vertebrae, wrists and hips.

Because of experience with very large doses of estrogen in former contraceptive pills or for treatment of prostatic cancer, it was feared that postmenopausal estrogen replacement would also increase the risk of myocardial infarction or stroke. Recent studies, however, show that the doses used for postmenopausal replacement therapy actually *reduce* this risk. In fact, estrogen-treated women have only 43% the risk of dying of myocardial infarction that occurs in comparable, but untreated, women.[16] The recent Lipid Research group study of the National Heart, Lung, and Blood Institute, National Institutes of Health, showed that the overall mortality of estrogen-treated women is only 37% of that found in untreated comparable women, in part because of a rise in protective high-density lipoprotein levels.[17]

I have long advocated estrogen replacement therapy for menopausal women to prevent vaginal atrophy, dyspareunia, bone loss with deformity and fractures and, in general, to add life to years. It is now also apparent that this treatment adds years to life.

DR SMITH: *Dr Gordan has given us a persuasive summary of the evidence that estrogen therapy can prevent the progressive bone loss characteristics of postmeno-*

pausal osteoporosis and therefore prevent its severe and often life-threatening complications. But what of the dangers of long-term use of exogenous estrogens? Dr Philip Hoffman will review this important topic for us.

Risks of Menopausal Estrogen Therapy

DR HOFFMAN:* Since 1977 the Food and Drug Administration has required that every woman given a prescription containing estrogen be given an information sheet describing the possible complications of estrogen therapy.[18] The most important of these are listed in Table 1.

There is no doubt that estrogen taken in sufficient doses for enough time at the appropriate age can cause all of these complications in women. The pertinent issue, however, is the risk incurred by a woman receiving estrogen in doses appropriate for preventing osteoporosis.

The incidence of cholecystitis is increased 2.0-fold to 2.5-fold by either oral contraceptive or menopausal estrogen therapy.[19] The other disorders listed in the table appear in roughly the order of our epidemiologic knowledge about them, the information on endometrial carcinoma being the most extensive.

TABLE 1.—*Risks of Estrogen Therapy*

Endometrial carcinoma	Subarachnoid hemorrhage
Breast cancer	Thromboembolism
Ischemic heart disease	Cholecystitis

TABLE 2.—*Incidence of Endometrial Cancer**

Therapy	*Patient-Years*	*Cancers*	*Incidence Per 1,000*
Untreated	2,477	6	2.42
Estrogen	2,302	10	4.34
Estrogen-progestin	7,063	5	0.71

*Adapted from Gambrell.[29]

Endometrial Carcinoma

A postmenopausal woman's risk of endometrial carcinoma developing is about 1 in 1,000 per year. Beginning in 1975 a series of published retrospective studies estimated the relative risk of endometrial carcinoma for women using estrogen to be 2 to 18 times that of nonusers.[20-23] Horwitz and Feinstein have argued that much of the apparent increased risk is attributable to more complete ascertainment of cancers in women undergoing dilatation and curettage for uterine bleeding than in largely uninvestigated control patients, but still found a relative risk of about 2.0.[24] In a recent series of 9,000 autopsies, endometrial carcinoma was four to five times as common as would have been expected in living patients, giving support to the contention that using controls from whom biopsy specimens were not taken overestimates relative risk.[25]

Accepting that postmenopausal estrogen administration does increase the risk of endometrial carcinoma, what does getting the cancer mean for a patient? For most women, it will mean a dilatation and curettage procedure, a hysterectomy and considerable physical and psychologic pain. For a few it will mean radiation therapy. The death rate has been studied by Collins and associates in 860 women, a third of whom had taken estrogen.[26] The five-year survival for those who had taken estrogen was 92% and for nonusers survival was 68%. Comparison with the appropriate age-specific survival rates for the general population of women indicated that the five-year survival rate for the estrogen-using cancer patients was virtually the same as for noncancer patients, whereas the survival for women who did not take estrogen was considerably less than for women of the same age at large. In another study, survival among estrogen-using cancer patients was actually significantly better than in the general population of the same age.[27]

Most of the improved survival among estrogen users is due to their tumors being better differentiated and less advanced. Whether this advantage is due entirely to earlier detection through better surveillance or to some other difference is not known.

In 1975 Gambrell started a prospective study of women being treated with sex hormones for menopausal symptoms.[28,29] To date more than 25,000 woman-years have been recorded. The women have largely chosen their own therapy from several options, and surveillance has been excellent (Table 2). In this study, the relative risk of endometrial carcinoma attributable to taking estrogen was about 2.0, as in the most optimistic retrospective studies. The most striking data, however, are those indicating that giving cyclic progestin along with the estrogen not only eliminated the increased risk of cancer due to estrogen, but actually decreased it below that found in untreated women. This observation has been confirmed by several independent reports, including a ten-year double-blind prospective study started in 1971.[30]

The treatment regimen recommended by Gambrell consists of giving estrogen for the first 25 days each month. A progestin is added on the 16th day and continued through the 25th day. No hormones are given between the 26th day and the end of the month. The usual estrogen dose is 0.6 mg of conjugated estrogens or 20 μg of ethinyl estradiol daily. Either norethindrone acetate, 5 mg, or medroxyprogesterone acetate, 10 mg, may be used as the progestin. Smaller doses of progestin would likely be equally satisfactory, but to obtain the degree of protection against endometrial carcinoma shown in Table 2, the progestin must be used for at least ten days each month.

Progestin probably diminishes the endometrial cancer risk by causing a virtually complete slough of the endometrium each month, thus preventing hyperplasia and

*Philip G. Hoffman, Jr, MD, PhD, Assistant Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco.

TABLE 3.—*Incidence of Breast Cancer in Postmenopausal Women**

Therapy	*Patient-Years*	*Cancers*	*Incidence Per 1,000*
Untreated	3,799	19	5.00
Estrogen	10,028	15	1.37
Estrogen-progestin	7,332	7	0.96

*Adapted from Gambrell.[29]

TABLE 4.—*Total Number of Deaths in Postmenopausal Women**

Treatment	*Patient-Years*	*Deaths*	*Incidence Per 1,000*
Untreated	9,386	63	6.71
Estrogen	3,401	9	2.65

*Adapted from Bush et al.[17]

neoplasia. Most postmenopausal patients will have light withdrawal bleeding with this regimen, creating a significant clinical management problem, but one that patient education can usually overcome.

For patients who find monthly withdrawal bleeding unacceptable, the extreme alternative of giving unopposed estrogen is not as great a risk as has been previously supposed. It is one that is defensible for a well-informed, well-monitored patient. The risk of dying from endometrial carcinoma if the progestin is omitted is certainly less than 0.4 per 1,000 per year and the total death rate is probably not significantly greater than for the general population, assuming any bleeding is investigated immediately.

Breast Cancer

Literally hundreds of papers have been written about the risk of breast cancer and estrogens. Breast cancer kills about 36,000 women in the United States each year, whereas endometrial cancer currently kills about 3,000, very few of whom have ever taken exogenous estrogens. A modest increase in the risk of breast cancer that would be difficult to prove in even a large study might be of extreme clinical importance. The relative risk of breast cancer due to menopausal estrogen therapy has been estimated in retrospective studies to range from 0.7 to 3.4, with most estimates clustering about 1.0. The highest estimated risks have usually been in small subsets of larger populations and the computation of confidence limits almost never included corrections for multiple comparisons.[31]

The only large prospective study with which I am familiar is Gambrell's study of the same cohort of women discussed with regard to endometrial cancer.[29]

The risk of 5 per 1,000 per year observed in the untreated population (Table 3) is close to the expected baseline rate for the postmenopausal population studied. The use of estrogen, with or without progestin, significantly diminished the occurrence of breast cancer. Other known risk factors were examined and could not account for the results. The primary weakness of the study is its relatively short duration, the maximum follow-up being nine years.

In summary, the current state of knowledge of the effect of menopausal estrogen replacement on breast cancer risk is that there are some prospective data that suggest a protective effect. Retrospective studies have not indicated that the risk ratio is other than 1.0. A small but clinically important increased risk has not been ruled out, but seems unlikely.

Cardiovascular Disease

The compelling data linking exogenous estrogen to various forms of cardiovascular disease can be divided into the following two types: studies of oral contraceptives in premenopausal women and studies of high doses of diethylstilbestrol (DES) in old men. Premenopausal women have lower risks of ischemic heart disease than do men of the same age, and this difference disappears gradually after menopause. In fact, this observation provided the rationale for some of the male diethylstilbestrol studies.

The doses of estrogen required for prevention of osteoporosis are smaller than those contained in oral contraceptives, and much lower than the equivalent doses of diethylstilbestrol studied in men.[32] The doses used for menopausal therapy have virtually no impact on clotting factors and have never been shown to have any effect on thrombotic phenomena.[19,33] The little that has been published on the effect of menopausal estrogen on stroke tends to show (but certainly does not prove) that treated women have fewer strokes.[34]

What has been shown is that conjugated estrogens in doses used for prevention of osteoporosis lower low-density lipoprotein and very low-density lipoprotein cholesterol while raising high-density lipoprotein (HDL) cholesterol (especially the HDL-2 fraction [density, 1.063 to 1.125 grams per ml]) in postmenopausal women.[29,35-37] Moreover, estrogen replacement in these doses seems to lower blood pressure slightly and decrease body weight.[38,39] Whether these reductions in risk factors translate into lowered risk of ischemic heart disease has yet to be proved, but evidence is growing that they do. Bain and associates found the relative risk of nonfatal myocardial infarction to be significantly reduced by the use of replacement estrogen among women who had had oophorectomies.[40] In a retrospective case-controlled study, Ross and colleagues found that the relative risk of fatal ischemic heart disease among postmenopausal women taking estrogen compared with controls was 0.43 (95% confidence interval, 0.24 to 0.75).[41] In a recent prospective report with an average of just over five years follow-up, Bush and co-workers found the age-adjusted risk of death from all causes for estrogen users among women aged 40 to 69 was only 0.37 (95% confidence interval, 0.17 to 0.79) times that for nonusers (Table 4).[17] Among women who had had oophorectomies, the protective effect of estrogen was even greater.

Conclusion

As the benefits of postmenopausal estrogen therapy for prophylaxis against osteoporosis become more ob-

vious, reassessment of the risks of such therapy is necessary for a physician to care appropriately for postmenopausal patients. Current data suggest that exogenous estrogen in doses appropriate for prevention of osteoporosis increases the risk of endometrial carcinoma less than was previously thought and does not increase the risk of dying from the disease. Moreover, the increased risk can be abolished by administering progestin. Estrogen therapy does not appear to increase the risk of breast cancer or cardiovascular disease, and there is preliminary evidence that treating women with estrogen may reduce age-specific mortality.

To help women make informed decisions about estrogen replacement therapy, a physician must place the well-publicized but often negligible risks of estrogen therapy in proper perspective and balance them against the substantial benefits such therapy provides.[42]

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